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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,289	01/16/2002	David E. Nichols	3220-69768	7025

7590 05/05/2004

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,289	NICHOLS ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Office Action of July 15, 2003 has been withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 4-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of treating Parkinson's disease comprising the steps set forth in claim 1 comprising administering "dinapsoline, dinoxyline, dihydrexidine", does not reasonably provide enablement for the term "D_1 agonist". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors**

have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating a patient with Parkinson's disease, comprising the steps of administering to the patient a full D_1 agonist wherein said agonist has a half-life of less than 6 hours and wherein said agonist is administered periodically at a dose resulting in a first tissue concentration of agonist capable of activating D_1 dopamine receptors to produce a therapeutic effect; and reducing said agonist dose at least once every 24 hours to obtain a second lower tissue concentration of agonist wherein said second concentration of agonist results in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance. The nature of the invention is extremely complex in that it encompasses the actual treatment of Parkinson's disease comprising the reducing D_1 agonist dose in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass treating a patient with Parkinson's disease, which has potentially many different causes (i.e. many different neuronal degradation or combination of degradations). Each of which may or may not be addressed by the administration of the claimed D_1 agonist with the method steps comprising suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually treat Parkinson's disease is minimal. All of the guidance provided by the specification is directed towards treatment with dinapsoline rather than any D_1 dopamine agonist.

Working Examples: All of the working examples provided by the specification are directed toward the treatment of Parkinson's disease with dinapsoline comprising suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance rather than any D_1 agonist.

State of the Art: While the state of the art is relatively high with regard to treatment of Parkinson's disease with a D_1 agonist with continual administration with optimal activation of D_1 receptors, the state of the art with regard to the concentration of agonist results in suboptimal activation of D_1 receptors is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to result in suboptimal activation of D1 receptors.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of Parkinson's disease comprising administering any D_1 agonist results in suboptimal activation with the claimed any D_1 agonist makes practicing the claimed invention unpredictable in terms of actual treatment of Parkinson's disease with suboptimal activation.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for treating Parkinson's disease comprising suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance.

If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to the treatment of Parkinson's disease comprising administering any D_1 agonist resulting suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance with any D_1 compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding the treatment of Parkinson's disease comprising administration of D_1 agonist result in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable

experimentation to practice the claimed invention comprising suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance in a subject by administration of any D_1 agonist. Therefore, a method of treating Parkinson's disease in a subject comprising administering any D_1 agonist resulting suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance is not considered to be enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "full D_1 agonist" is indefinite since it is not clear what is meant by the term to be encompassed thereby without clear definition in the specification.

The remaining claims 4-12 are indefinite to the extent that they depend from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1,2 and 4-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S.Patent No. 6,194,423) in view of Taber et al. (XP-002231341) of record.

Nichols et al. teach the compounds (dinapsoline and dihydrexidine) are useful for the treatment of Parkinson's disease. (abstract, column 6, line 56-column 7, particularly lines 39-45). Nicholes et al. teach the compounds can be administered as an oral, injectable and other dosage forms. (column 5, lines 21-46). Nicholes et al. teach the compounds can be formulated with adjuvants such as wetting agents, emulsifying and suspending agents, sweetening and flavoring agents and other excipients. (column 5, lines 25-40). Nicholes et al. teach the compounds can be administered in daily single dose or multiple doses per day. (column 5, lines 15-21).

Nicholes et al. do not teach the specified method comprising reducing the dose of D1 agonist at least once every 24 hours to obtain a second lower tissue

concentration of agonist to prevent induction of tolerance by suboptimal activation of D1 dopamine receptors for a period of time sufficient to prevent induction of tolerance.

Taber et al. teach that the dopamine D1 receptor agonist, dinapsoline can be administered subcutaneously and orally and it has an impact on development of tolerance.

It would have been obvious to one of ordinary skill in the art to modify Nicholes et al' daily dosing of full dopamine agonist (e.g. dinapsoline and dihydrexidine) by decreasing dose to reduce tolerance because Taber et al. teach that the dopamine D1 receptor agonist, dinapsoline has an impact on development of tolerance. One would have been motivated to optimize the daily dosing including singular or multiple daily regimens taught by Nicholes et al. to achieve optimum dosage regimen by reducing the required dose to avoid the development of tolerance in Parkinson's disease patient of Nicholes et al.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

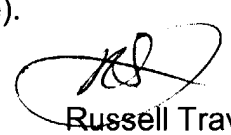
Applicants' arguments and the declaration of Dr. Mailman filed on January 20, 2004 have been carefully considered but they are not persuasive. Applicants essentially argue the working example provided by the exemplification of the full D1

agonist dinapsoline is generally illustrative of the invention, which included administering a full D1 agonist in method for treating Parkinson's disease and full D1 agonist behave functionally as dopamine and have half-lives of less than 6 hours. Further, the data discussed in the declaration demonstrate that by using the experimental design described in the captioned application (i.e. the guidance of specification), Dr. Mailman showed that other full D1 agonists from other chemical classes can be used in the claimed method. This is not persuasive because an enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation" and the amount of direction or guidance provided can only be described as meager. According to the specification the regimen and particular dosage of dinapsoline but yet the claims are drawn to any full D1 agonist. There is no evidence that any full D1 agonist would prevent tolerance by the method set forth in the claims. It is noted that the declaration only shows the data of the specific full D1 agonist therein not for all and any full D1 agonist. Therefore, a method of treating Parkinson's disease in a subject comprising administering any D1 agonist resulting suboptimal activation of D1 dopamine receptors for a period of time sufficient to prevent induction of tolerance is not considered to be enabled by the instant specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Russell Travers
Primary Examiner
Art Unit 1617

Jmk
April 30, 2004